THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 40

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ARNOLD BROSSI, MALGORZATA BRZOSTOWSKA, S. RAPOPORT, and NIGEL GREIG

Appeal No. 95-3117
Application 08/096,207[1]

ON BRIEF

Before WINTERS, GRON, and PAK, Administrative Patent Judges.

GRON, Administrative Patent Judge.

DECISION ON APPEAL UNDER 35 U.S.C. § 134

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[1] Application for patent filed July 26, 1993. According to applicants, this application is a continuation of Application 07/861,329, filed March 31, 1992, now abandoned;
which is a continuation-in-part of Application 07/765,746, filed September 26, 1991, now U.S. Patent No. 5,171,750.

This is an appeal under 35 U.S.C. § 134 of an examiner's rejection of Claims 23, 24, 28, 29, 34-37, 43, and 46. The examiner allowed Claims 47-53 (Paper No. 26), the only remaining claims in this application.

Introduction

Claims 23, 24, 28, 29, 34-37, 43, and 46 stand rejected under 35 U.S.C. § 103 as being unpatentable in view of the combined teachings of Yu et al. (Yu I), "Carbamate Analogues of (-)-Physostigmine: In Vitro Inhibition of Acetyl- and Butyrylcholinesterase," FEBS Letters, Vol. 234, No. 1, pp. 127-130 (July 1988); Glamkowski et al. (Glamkowski), U.S. 5,081,117, patented January 14, 1992, filed November 3, 1989, and Yu et al. (Yu II), "Synthesis and Anticholinesterase Activity of (-)-*N*[1]-Norphysostigmine, (-)-Eseramine, and Other N(1)-Substituted Analogues of (-)-Physostigmine," J. Med. Chem., Vol. 31, No. 12, pp. 2297-2300 (1988). Claims 23, 24, 28, 29, 34-37, 43, and 46 also stand rejected under 35 U.S.C. § 103 as being unpatentable in view of the combined teachings of Yu I, Glamkowski, Yu II, and Albuquerque et al. (Albuquerque), "Multiple Actions of Anticholinesterase Agents on Chemosensitive Synapses: Molecular Basis for Prophylaxis and Treatment of Organophosphate

Poisoning," Fundam. Appl. Toxicol., Vol. 5, pp. S182-S203 (1985). Claims 23 and 28 are representative of the subject matter claimed and read:

> 23. A compound for the selective inhibition of acetylcholinesterase selected from the group consisting of:
> (-)-2'-methylphenylcarbamoyleseroline (1),
> (-)-2'-methylphenylcarbamoyl-N1-noreseroline (11),
> (-)-phenylcarbamoyl-N1-noreseroline (14),
> and pharmaceutically acceptable salts thereof.
>
> 28. A method for inhibiting acetylcholinesterase activity comprising administering an effective amount of at least one compound according to claim 23 to a mammal in need thereof.

Discussion

We have considered the entire record, including the claims on appeal; the supporting specification; the Appeal Brief; the Examiner's Answer; the Reply Brief; the teachings of Yu I, Glamkowski, Yu II, and Albuquerque; and the Declarations of Dr. Arnold Brossi, signed May 19, 1994, and Dr. Nigel H. Greig, signed June 23, 1993. We have also considered Brzostowska et al. (Brzostowska), "Phenylcarbamates of (-)-Eseroline, (-)-*N*[1]-Noreseroline and (-)-Physovenol: Selective Inhibitors of Acetyl and, or Butyrylcholinesterase," Med. Chem. Res.,

Vol. 2, pp. 238-246 (1992); Flippen-Anderson et al. (Flippen-Anderson), "Thiaphysovenol Phenylcarbamates: X-Ray Structures of Biologically Active and Inactive Anticholinesterase Agents," Heterocycles, Vol. 36, No. 1, pp. 79-86 (1993); Atack et al. (Atack), "Comparative Inhibitory Effects of Various Physostigmine Analogs Against Acetyl- and Butyrylcholinesterases," J. Pharmacol. Exp. Ther., Vol. 249, No. 1, pp. 194-202 (1989);

Hamer et al. (Hamer), EP-253,372, published January 20, 1988; Yu et al. (Yu III), "Practical Synthesis of Unnatural (+)-Physostigmine and Carbamate Analogues," Heterocycles, Vol. 27, No. 3, pp. 745-750 (1988); Yu et al (Yu IV), "73. Physovenines: Efficient Synthesis of (-)- and (+)-Physovenine and Synthesis of Carbamate Analogues of (-)-Physovenine. Anticholinesterase Activity and Analgesic Properties of Optically Active Physovenines," Helv. Chim. Acta, Vol. 74, pp. 761-766 (1991); Pomponi et al. (Pomponi), EP-154,864, published September 18, 1985; and Chem. Abst., Vol. 110, No. 9, Abst. No. 69253s, "New Analogs of Physostigmine; Alternative Drugs for Alzheimer's Disease," p. 41 (February 27, 1989).

We review the examiner's rejections presuming *a priori*

that the combined teachings of the applied prior art references establish a case of *prima facie* obviousness of the subject matter of Claims 23, 24, 28, 29, 34, 35, and 36 and the separately considered subject matter of Claims 37, 43, and 46 under 35 U.S.C. § 103. The presumption reasonably appears to be justified in light of the combined prior art teachings of active *N*-phenylcarbamoyl eseroline and substituted phenylcarbamoyl eserolines in Yu I (Yu I, p. 128, Table 1, Nos. 3, 4, and 5), comparative activities for eserolines and noreserolines in Yu II (Yu II, p. 2297, Table I), and the activity of related "aryl" carbamates and compositions therewith wherein "aryl" may be "phenyl, o-tolyl, m-methoxyphenyl, etc." reported by Glamkowski (Glamkowski, col. 2, l. 26-27). However, we reverse the examiner's rejections based on our findings that the evidence of record shows unexpected properties for the three specific compounds appellants claim on appeal relative to the closest prior art active compounds, namely *N*-phenylcarbamoyl, methoxyphenylcarbamoyl, and chlorophenylcarbamoyl eserolines.

The examiner was not persuaded by the comparative results

reported in Table 2 in the specification for the following reasons (Examiner's Answer, pp. 5-6):

> Appellant's [sic] arguments regarding the data of Table 1 [of Yu I] have been carefully considered. The arguments focus on the selectivity of the claimed compounds, urging that such selectivity is not found in the compounds of the prior art. However, the prior art compounds are seen to possess selectivity also. For example, Yu (I) compound 3 is selective for AChE. Because it is known in the art that such compounds may selectively inhibit one type of cholinesterase over another, such selectivity does not render the instant compounds patentable over the prior art.
>
> Further, the differences in such selectivity are not seen to be as great as appellant urges. Given the margins of error involved, the differences in selectivity between compound D' of Yu [(Compound "D' phenserine" in appellants' Table 2 on page 26 of the specification corresponds to compound No. 3 N-phenylcarbamoyl eseroline in Table 1 of Yu I).] and compound 1 herein may be as little as 6.1 nmol/318 nmol, for AChE and BChE inhibiting activity, respectively.
>
> Likewise, the differences are 0.8 nmol/43 nmol for compound 11 versus compound D' of Yu. In fact, given the margin of error, the BChE inhibition of compound 11 is within the range of compound D'. Thus, the differences are not deemed to be as great as to be unexpected.
>
> As regards the data presented to rebut the obviousness raised by the art with respect to compound 14, the data of Table 2 has been considered to be insufficient. The difference in activity between the two comounds [sic] is

> not so great as to be unexpected. The AChE activity of the instantly claimed compound is 13.8 ± 0.7 nmol, while the activity of the reference comound [sic] is 24 ± 6 nmol.
>
> Given the margin of error in the figure for the Yu compound, the difference in activity could be as slight as 3.5 nmol. Such a difference in activity is not so great as to be considered unexpected.

In our view, the examiner's findings and conclusions result from her failure to consider all that Yu I teaches. The examiner must consider all the evidence on the question of obviousness. In re Sernaker, 702 F.2d 989, 996, 217 USPQ 1, 7 (Fed. Cir. 1983).

In considering whether the subject matter appellants claim would have been obvious to a person having ordinary skill in the art, the examiner must first determine what results the combined prior art teachings as a whole would have led persons having ordinary skill in the art reasonably to expect when using the compounds, compositions, and methods appellants claim. The expected results are then compared to the results applicants report. See In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988):

> [T]he full field of the invention must be considered; for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that

> which might lead away from the claimed invention. . . . Evidence that supports, rather than negates, patentability must be fairly considered.

We revisit the teaching of Yu I, aside from the results appellants alone disclose, and consider Yu's own analysis of the results he discloses. "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." Id. at 473, 5 USPQ2d at 1531.

Yu I concludes, based on test results reported for active (-)-physostigmine, *N*-phenylcarbamoyl eseroline, benzylcarbamoyl eseroline, methoxyphenylcarbamoyl eseroline, and chlorophenyl-carbamoyl eseroline (Yu I, p. 128, Table 1, Nos. 2, 3, 8, 4, and 5) that (Yu I, p. 128, col. 2, to p. 129, col. 2, bridging para.; emphasis added):

> None of the (-)-physostigmine derivatives studied was as potent against electric eel AChE as (-)-physostigmine itself. . . . [L]engthening of the carbamoyl side chain does not greatly reduce the ability of the carbonyl group to interact with the esteratic site of electric eel AChE. However, the addition of either N-phenyl or benzyl group reduces the potency of the resulting compounds (*N*-phenyl-carbamoyl eseroline (**3**) and benzylcarbamoyl eseroline (**8**)) much more . . . indicating that the bulk of these groups

> reduces the interaction between the carbonyl group and the esteratic site. Indeed, when the bulk of the phenyl group is further increased by the addition of either a chlorine atom or a methoxy group, the potency of the resulting compounds (chlorophenylcarbamoyl eseroline (**5**) and methoxyphenylcarbamoyl eseroline (**4**), respectively) is reduced approx. 5-fold compared to phenylcarbamoyl eseroline (**3**) and to less than 5% of (-)-physostigmine. Compounds with very bulky carbamoyl side chain additions, such as *N*-benzyl-*N*-methylallophanyl eseroline (**12**) and *N*-dibenzylallophanyl eseroline (**13**), showed low anti-AChE potencies (relative potency <1%).

Based on Yu's analysis of his own work, we fail to see why persons having ordinary skill in the art reasonably would have been led to expect (-)-2'-methylphenylcarbamoyl eseroline or (-)-2'-methylphenylcarbamoyl noreseroline with bulky methylphenylcarbamoyl groups to be as potent as *N*-phenylcarbamoyl eseroline versus electric eel AChE. Yu I appears to predict the opposite result, i.e., potency inferior to *N*-phenylcarbamoyl eseroline versus electric eel AChE. In light of (1) the Yu I report of a 5-fold reduction of activity for substituted-phenylcarbamoyl eseroline as compared to *N*-phenylcarbamoyl eseroline and an activity of less than 5% of (-)-physostigmine and (2) the Yu II report showing comparable potencies of eserolines and noreserolines, we find that

appellants' showings that the potency of each of the presently claimed compounds is at least superior to (-)-physostigmine are unexpected and strongly support patentability over the combined prior art teachings.

Appellants' citation of Atack should have erased any difficulty persons having ordinary skill in the art might have had in comparing appellants' showing of potencies toward human erythrocyte AChE and human plasma BChE to the comparative potencies Yu I tabulates for electric eel AChE and human plasma BChE (Yu I, p. 128, Table 1). Note the final comments of Yu I (Yu I, p. 130, col. 2):

> . . . whether the differences in potencies toward AChE and BChE observed in the present report are due to the compounds themselves or are merely a consequence of interspecies variability (i.e., is this same pattern of inhibitory properties seen in AChE and BChE derived from the same species?)

While Atack shows that Yu's suspicions with regard to interspecies potency variabilities were correct and that *N*-phenylcarbamoyl eseroline is more potent against human erythrocyte AChE than (-)-physostigmine and less potent against electric eel AChE than (-)-physostigmine, we find that appellants' results are no less significant and unexpected (Atack, p. 198, Table 1). In either case, Atack shows that

substituted-phenylcarbamoyl eserolines were comparatively far less potent than *N*-phenylcarbamoyl eseroline, the closest prior art compound. Applicants unexpectedly found that the claimed compounds were at least markedly superior to *N*-phenylcarbamoyl eseroline in their potencies toward human erythrocyte AChE. Whether considering the compounds' potencies toward electric eel or human erythrocyte AChE, we find that persons having ordinary skill in the art would have expected inferior results using the compounds of the claims on appeal.

Not only does the examiner criticize the unexpected character of appellants' showing of AChE selectivity (Ans., p. 6), she belittles appellants' argument that AChE selectivity can patentably distinguish compounds active against both AChE and BChE (Ans., pp. 5-6, bridging para.):

> The arguments focus on the selectivity of the claimed compounds, urging that such selectivity is not found in the compounds of the prior art. However, the prior art compounds are seen to possess selectivity also. For example, Yu (I) compound 3 is selective for AChE. Because it is known in the art that such compounds may selectively inhibit one type of cholinesterase over another, such selectivity does not render the instant compounds patentable over the prior art.

We do not understand the examiner's position. Yu I

acknowledges that persons skilled in the art had sought to obtain "compounds that might be non-clinically more useful (i.e., longer biological half-life, better specificity for AChE rather than BChE) than (-)-physostigmine" (Yu I, p. 127, col. 1, and p. 128, Table 1, "IC_{50} BChE/IC_{50} AChE"). The degree of selectivity is patentably significant indeed. See In re Papesch, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963)("From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same. . . . There is no basis in law for ignoring any property in making . . . a comparison. An assumed similarity based on a comparison of formulae must give way to evidence that the assumption is erroneous.") On consideration of all the evidence, especially the significant properties of the compounds claimed, we reverse the examiner's rejection.

However, the examiner may wish to give Atack's teaching a closer look, especially Atack's discussion at pages 198-201 (**Carbamoyl-substituted analogs.**) of the expected effect of increasing the hydrophobicity of the carbamoyl side group on the potency of a compound toward human and eel AChE and BChE. We decline to decipher this teaching *de novo*. See In re Hoch,

428 F.2d 1341, 1342 n. 3, 166 USPQ 406, 407 n. 1 (CCPA 1970) ("Where a reference is relied on to support a rejection, whether or not in a "minor capacity," there would appear to be no excuse for not positively including the reference in the statement of the rejection.")

Conclusion

We reverse all the examiner's rejections of Claims 23, 24, 28, 29, 34-37, 43, and 46 under 35 U.S.C. § 103.

REVERSED

Sherman D. Winters Administrative Patent Judge	)	
Teddy S. Gron Administrative Patent Judge	)	BOARD OF PATENT APPEALS AND INTERFERENCES
Chung K. Pak Administrative Patent Judge	)	

tdc

Appeal No. 95-3117
Application 08/096,207

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